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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,474	05/17/2005	Wolfgang Richter	63419(52171)	4298

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EXAMINER	
KOSACK, JOSEPH R	

ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,474	RICHTER ET AL.	
	Examiner	Art Unit	
	Joseph R. Kosack	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-24 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-24 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

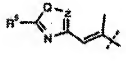
Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 12-24 and 26-30 are pending in the instant application.

Previous Claim Rejections - 35 USC § 112

Claims 12-24 were rejected in the previous action under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Applicant has traversed the rejection on the grounds that the written description has details about the compounds as well as a number of synthesis examples. This is not found to be persuasive as all the synthesis examples are drawn to where A is  . While the ring structure may be modified to include additional rings, the synthetic examples provided only show the olefin connecting the thiazole ring to the thia-epothilone ring. At most, the scope of supported subject matter could extend to compounds where A is  , but from the synthesis examples disclosed, there is no guidance provided in order to make the compounds with a different A group. Additionally, Applicant has not pointed to where the "extensive number of synthesis examples" are in the application as the examples are drawn to a small number of thiaepothilones with the exact same A group. Therefore, the compounds are still not adequately described and one of skill in the art would not find that the Applicant was in possession of the entire claimed scope at the time of filing. The rejection is maintained.

Claims 22-23 were rejected in the previous action under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some cancers,

does not reasonably provide enablement for treating all cancers. Applicant has traversed the rejection on the grounds that the specification details the therapeutic uses of the compounds and that no evidence was advanced as to why one skilled in the art would not be able to make and use the claimed invention. This is not found to be persuasive because the disclosure only details how to treat cure in an extremely general fashion when it is known in the art that different cancers react differently to different drugs. Additionally, the Examiner made a case citing literature references for lack of enablement in the previous action and copies of those references were forwarded to the Applicant in that action. Therefore, the decision of In re Marzocchi has been addressed since the Examiner explained why and rejection is maintained.

Previous Claim Rejections - 35 USC § 103

Claims 12-23 and 25 were rejected in the previous action under 35 U.S.C. 103(a) as being obvious over Nicolaou et al. (*Angew. Chem. Int. Ed. 1998*, 2014-2045) in view of Patani et al. (*Chem. Rev. 1996*, 3147-3176). Applicant has traversed the rejection on the grounds that Patani et al. is merely a background article and provides no motivation sufficient to sustain the rejection and that the rejection mirrors the decision of the CAFC in *In re Grabiak*. This is not found to be persuasive as while Patani et al. is a review article, the motivation to make the bioisosteric changes within the article is provided in the beginning of the article where Patani et al. states that "Bioisosterism represents one approach used by the medicinal chemist for the *rational* modification of lead compounds into safer and more clinically effective agents." (emphasis added) Therefore, motivation to combine is present. The instant case is different from *In re Grabiak* in that a

reference *has* been cited to suggest the change. In fact, the instant *prima facie* case of obviousness meets the test set out by the court of *In re Graviak* as the reference teaches the modification and why those modifications are made in the pharmaceutical art. The rejection is maintained except for claim 25 which has been cancelled.

Previous Double Patenting Rejections

Claims 12-23 and 25were provisionally rejected in the previous action on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 11 of copending Application No. 10/520,769, now published as UPSN 20060004065 A1 in view of Patani et al. (*Chem. Rev. 1996*, 3147-3176). The traversal by the Applicant is on the same grounds as the traversal of the 35 U.S.C. 103(a) rejection and the Examiner's reply is the same as detailed above for the 35 U.S.C. 103(a) rejection. The provisional rejection is maintained except for claim 25 which has been cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-24 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant case, compounds of formula I are claimed to have a heteroalkyl, heterocycloalkyl, heteroalkylcycloalkyl, heteroaryl, or a heteroarylalkyl group.

The specification fails to teach compounds covering the entire scope of the claimed invention. For example, the only example of an A group within the working examples in the specification is:  . Additionally, for new claim 24, there is no example of just a thiazole ring in the A position, the olefin linker is always present. Therefore, a person of skill in the art would deem that the Applicant did not possess the entire invention as claimed at the time of filing, and claims 12-24 do not meet the written description portion of 35 U.S.C. 112, first paragraph. Applicant is encouraged to limit the substituent groups to be consistent with those fully supported by the specification.

Claims 12-24 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant case, compounds of formula I are claimed to have a heteroalkyl, heterocycloalkyl, heteroalkylcycloalkyl, heteroaryl, or a heteroarylalkyl group.

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no example of just a thiazole ring in the A position, the olefin linker is always present. Therefore, a person of skill in the art would deem that the Applicant did not possess the entire invention as claimed at the time of filing, and claims 12-24 do not meet the written description portion of 35 U.S.C. 112, first paragraph. Applicant is encouraged to limit the substituent groups to be consistent with those fully supported by the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-24 and 26-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for solvates in the solution phase, does not reasonably provide enablement for solvates in the isolatable or solid form. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims listed above are drawn not only to the compounds themselves, but also to solvates and hydrates thereof. The current skill in the art is that the existence and physical properties of isolatable or solid form solvates and hydrates is unpredictable. See Hildesheim et al., USPN 7,056,942, column 2, line 66 through column 3, line 5. Additionally, there are no examples present within the specification that teach a solid form solvate or hydrate. The term solvate as defined encompasses both solution-phase and isolatable solvates (pages 9-10 of the specification.)

Therefore, on the virtue of the evidence above, it would require undue experimentation for one of skill in the art to make the solid and isolatable solvates that are claimed instantly.

Claims 22, 23, 29, and 30 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some cancers, does not reasonably provide enablement for treating all cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

.

The Nature of the Invention

The nature of the invention is the treatment of all cancers (Claims 22-23).

The State of the Prior Art and the Predictability or Lack Thereof in the Art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even

in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Nicolaou et al. (*Angew. Chem. Int. Ed. 1998*, 2014-2045) teach that epithilones A-E along with structural analogs synthesized by the group are effective in inhibiting ovarian and breast cancer cell lines (Table 7, page 2041). Nicolaou et al. do not teach any testing or effectiveness of analogs of epithilones A or B with other types of cancer cell lines.

Flörsheimer et al. (*Expert Opin. Ther. Patents 2001*, 951-968) teach that it is too early to judge whether or not epothilone-based agents will one day be clinically useful anti-cancer drugs (page 965, column 2, last paragraph). Flörsheimer et al. do teach though that naturally occurring epothilones are effective in inhibiting net growth of certain human cancer lines (page 952, Table 1).

Hence, in the absence of a showing of correlation between all cancers claimed as capable of treatment by the claimed compounds, one of skill in the art is unable to fully predict possible results from the administration of the compound of formula 1 due to the unpredictability of the role of those compounds in treating all cancers, and the

unpredictability of the ability of the compound of formula 1 to cause toxicity or any improvement in condition.

The Amount of Direction or Guidance Present and the Presence or Absence of Working Examples

The specification does not show any in vitro or in vivo data of the compounds. The specification directs the person of ordinary skill in the art to consult the two references cited in the previous section for guidance in the treatment of all cancers.

The Breadth of the Claims

The breadth of the claims is the treatment of all cancers (Claims 22-23).

The Quantity of Experimentation Needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which cancers can be treated with the compounds of the instant invention, dosages, the method of drug delivery, and any potential combination therapies.

The Level of Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of formula 1 for the treatment of all cancers. As a result, necessitating one of skill to perform an exhaustive search for which cancers can be treated by what compounds of formula 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

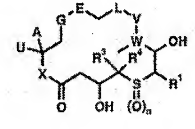
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-23 and 26-30 rejected under 35 U.S.C. 103(a) as being obvious over Nicolaou et al. (*Angew. Chem. Int. Ed. 1998*, 2014-2045) in view of Patani et al. (*Chem. Rev. 1996*, 3147-3176).

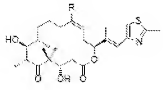
The instant application is drawn to compounds of the formula:



with substitutions as defined along with a method of treating cancer with the compounds.

Determination of the scope and content of the prior art (MPEP §2141.01)

Nicolaou et al. teach Epopthilone D which as the structure of



where R is methyl. Nicolaou et al. also teach the use of epothilones to treat cancer by killing tumor cells through a mechanism similar to paclitaxel. See page 2016.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Nicolaou et al. do not teach a thioether or a SO_2 in place of the carbonyl next to the gem-dimethyl of the epothilone ring.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Patani et al. teach that carbonyl can be replaced by S, SO, or SO_2 if the position is not essential to the function of the molecule. See page 3167, Figure 67, Table 39, and the last paragraph of column 1.

Nicolaou et al. teach that when the carbonyl at the C5 position is reduced, potency of the epothilone was reduced. See page 2040, column 1, third paragraph. However, Nicolaou do not show any compounds or activites of compounds with a reduced ketone in the C5 position in the Table 5 cited by the passage. Therefore, the person of ordinary skill would determine that the position is non-essential to the function of the compound, and may be modified by the advice of Patani et al.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to follow the synthetic scheme of Nicolaou et al. with the replacement suggested by Patani et al. to make the claimed invention. The

motivation to do so is provided by Nicolaou et al. Nicolaou et al. teach the use of the compounds as killers of tumor cells. See page 2016.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

Double Patenting

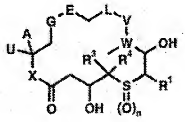
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

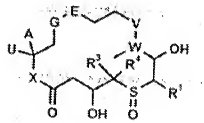
Claims 12-23 and 26-30 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 11 of copending Application No. 10/520,769, now published as UPSN 20060004065 A1 in view of Patani et al. (*Chem. Rev. 1996*, 3147-3176).

The instant application is drawn to compounds of the formula:



with substitutions as defined along with a method of treating cancer with the compounds.

Determination of the scope and content of the prior art (MPEP §2141.01)

'769 teaches compounds of the formula  with substitutions as defined.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

'769 does not teach a S or SO_2 in place of the SO group in the compound.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Patani et al. teach that carbonyl can be replaced by S, SO, or SO_2 if the position is not essential to the function of the molecule. See page 3167, Figure 67, Table 39, and the last paragraph of column 1.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to follow the synthetic scheme of '769 with the replacement suggested by Patani et al. to make the claimed invention. The motivation

to do so is provided by '769. '769 teaches the use of the compounds to treat cancer. See claim 11.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Claims 12-24 and 26-30 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph R. Kosack whose telephone number is (571)272-5575. The examiner can normally be reached on M-Th 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1626

/Joseph R Kosack/
Examiner, Art Unit 1626